

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :  
Yoshikazu UENO et al. :  
Serial No. NEW : **Attn: APPLICATION BRANCH**  
Filed December 12, 2003 : Attorney Docket No. 2003-1812

PROCESS FOR THE PREPARATION OF  
1,2-DICHLOROETHANE FREE  
CRYSTALS OF ZONISAMIDE  
(Rule 1.53(b) Continuation of Serial No.  
10/462,595, Filed June 17, 2003)

THE COMMISSIONER IS AUTHORIZED  
TO CHARGE ANY DEFICIENCY IN THE  
FEE FOR THIS PAPER TO DEPOSIT  
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**INFORMATION DISCLOSURE STATEMENT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Pursuant to the provisions of 37 CFR 1.56, 1.97 and 1.98, Applicants request consideration of [X] the references listed on attached form PTO-1449 and/or [X] the additional information identified below in paragraph 3. A legible copy of each reference listed on the form PTO-1449 was previously cited by or submitted to the Patent Office in prior parent application Serial No. 10/340,601.

1a. [X] This Information Disclosure Statement is submitted:

within three months of the filing date (or of entry into the National Stage) of the above-entitled application, **or**

before the mailing of a first Office Action on the merits or the mailing of a first Office Action after the filing of an RCE,

**and thus no certification and/or fee is required.**

1b. ☐ This Information Disclosure Statement is submitted

after the events of above paragraph 1a and prior to the mailing date of a final Office Action or a Notice of Allowance or an action which otherwise closes prosecution in the application, and thus:

(1) ☐ the certification of paragraph 2 below is provided, **or**

(2) ☐ the fee of \$180.00 specified in 37 CFR 1.17(p) is enclosed.

1c. ☐ This Information Disclosure Statement is submitted:

after the mailing date of a final Office Action or Notice of Allowance or action which otherwise closes prosecution in the application, and prior to payment of the issue fee, and thus:

**the certification of paragraph 2 below is provided, and**

**the fee of \$180.00 specified in 37 CFR 1.17(p) is enclosed.**

2. It is hereby certified

a. ☐ that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the Statement, or

b. ☐ that no item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of the person signing the certification after making reasonable inquiry, was known to any individual designated in §1.56(c) more than three months prior to the filing of the Statement.

3. ☒ Consideration of the following list of additional information (including any copending or abandoned U.S. application, prior uses and/or sales, etc.) is requested.

The process of the present application was confidentially disclosed to the Food and Drug Administration (FDA) more than one year before the effective filing date of the present application, in connection with an approved New Drug Application (NDA) for zonisamide.

4. For each non-English language reference listed on the attached form PTO-1449, reference is made to:
- a. ☒ a full or partial English language translation of record in the prior parent application,
  - b. ☐ a foreign patent office search report (in the English language) submitted herewith,
  - c. ☒ the concise explanation contained in the specification of the present application at pages 1, 2, 10 and 11,
  - d. ☒ the concise explanation set forth in the English language abstract of record in the prior parent application,
  - e. ☒ the concise explanation set forth below or on a separate sheet attached to the reference:

The Uno et al. reference (USP 4,172,896), which is cited on page 1 of the present specification, discloses compounds of formula (I) which includes zonisamide, and which is specifically named at column 2, line 16 (3-sulfamoylmethyl-1,2-benzisoxazole). The solvents used in preparing the compounds of formula (I) are disclosed at column 2, lines 40-49, and the solvents used in preparing the intermediate of formula (II) are disclosed at column 3, lines 17-18. None of these solvents include 1,2-dichloroethane. Therefore, it is quite apparent that the zonisamide final product of this reference will not contain any residual 1,2-dichloroethane, to which the present invention is directed.

The Chang et al. reference (USP 4,533,764), as indicated in the paragraph bridging pages 3 and 4 of the present specification, discloses a method of removing residual solvent by distillation in purification of bisphenols, wherein the solvent occluded in bisphenols is released and removed from bisphenol melted in water. This method utilizes the characteristic of bisphenol, which melts in water by heating, and thereby the occluded solvent is released. On the other hand, zonisamide cannot melt even by heating in water, and hence, this method cannot be applied for removal of the solvent occluded in crystals of zonisamide.

JP 53-77057 is cited on pages 1, 2, 10 and 11 of the present specification. In addition to the English abstract attached to the copy of this reference, there is also an English translation of process (c), Reference Examples 2 and 3 and Example 1. The compound produced in Example 1 is 3-sulfamoylmethyl-1,2-benzisoxazole, i.e. zonisamide. The solvent used in Example 1 in preparing the zonisamide is ethyl acetate. The intermediate used in Example 1 for the preparation of zonisamide is 1,2-benzisoxazole-3-methanesulfonyl chloride, prepared in Reference Example 2, which discloses the use of aqueous methanol as solvent. Therefore, it is apparent that the zonisamide of Example 1 of the reference does not contain any residual 1,2-dichloroethane solvent, to which the present invention is directed.

JP 54-163823, which is cited on page 1 of the present specification, discloses the preparation of zonisamide (the compound of formula (I)). However, 1,2-dichloroethane is not used as a solvent in the preparation of either the zonisamide final product, or the intermediate. Therefore, the reference does not disclose zonisamide containing residual 1,2-dichloroethane, to which the present invention is directed.

The Shimizu et al. reference, (Yakugaku Zasshi, 116 (7) 533-547 (1996)) is cited on page 1 of the present specification. As indicated by the partial English translation attached to this reference, and also toward the bottom of page 1 of the present specification, the solvent used in preparing the intermediate is dichloromethane, as also shown in Chart 4 on page 5 of the partial translation of this reference. Therefore, it is apparent that the reference does not disclose zonisamide containing residual 1,2-dichloroethane, to which the present invention is directed.

The "Impurities: Guideline for Residual Solvents" reference, which is cited on page 2 of the present specification, indicates the concentration limit of 1,2-dichloroethane in pharmaceutical products is 5 ppm (Table 1 on page 5 of the reference). The present invention is directed to zonisamide containing not more than 5 ppm.

Uno et al. (Chem. Pharm. Bull.) discloses a process for preparing zonisamide which is similar to that of Example 1 of JP 53-77057.

Uno et al. (Journal of Medicinal Chemistry) also discloses a process for preparing zonisamide which is similar to that of Example 1 of JP 53-77057.

JP 54-163570 (which is accompanied by an English abstract and translation of Reference Examples 1 and 2) discloses a process for preparing zonisamide which is similar to that of Reference Example 2 and Example 1 of JP 53-77057.

Applicants also note that the two latter Uno et al. references are cited as references 5 and 21 on page 545 of the Shimizu et al. reference.

WO 03/020708 was published March 13, 2003, after Applicants' parent U.S. filing date of January 13, 2003, and is based on two U.S. applications filed in 2001. The reference is being cited because claim 4 discloses dichloroethane as an organic solvent (for the preparation of an intermediate of zonisamide).

JP 63-150220, which is commonly assigned with the present application, discloses, based on the abstract attached to the reference, mixing zonisamide with a powdery substance capable of shielding disagreeable taste and an organic solvent which dissolves the powdery substance and preferably does not dissolve the drug. The organic solvents are exemplified by ethanol, chloroform, and acetone. After granulation, the organic solvent is removed.

The abstract fails to disclose or suggest zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane of the present invention.

FR 2 428 033 is also commonly assigned with the present application. The reference corresponds to USP 4,172,896, discussed above, and such comments distinguishing the present invention from US '896 are equally applicable to distinguishing the present invention over the FR '033 reference.

Lemmens et al. discloses a process for making spherical pellets by combining a solvent, a pharmaceutically active agent and at least one pellet forming carrier to form a wet mixture, stirring the wet mixture to form monolithic, spherical wet pellets, and drying the wet pellets to form pharmaceutically acceptable pellets.

[0046] on page 5 discloses that the solvent is typically water, but any liquid can be used including organic solvents such as ethanol; and this paragraph also discloses zonisamide among the active agents.

However, there is no disclosure or suggestion in the reference of zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane, to which the present invention is directed.

Jennings discloses the use of zonisamide for treating headaches. It does not specifically disclose any process for preparing the zonisamide, but paragraph [0008] on page 1 incorporates by reference USP 4,172,896, discussed above.

The reference does not disclose or suggest zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane.

Nakamichi et al. discloses a method of using an extruder to induce a transition from one crystalline state to another crystalline state in a crystallizable medicinal substance. Zonisamide is specially mentioned as a crystallizable medicinal substance, at column 6, line 59.

However, there is no disclosure or suggestion in the reference of zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane.

Farooq et al. discloses benzisoxazole derivatives, a process for the preparation thereof, and the use thereof in fungicidal and pesticidal compositions. The benzisoxazole derivatives (formula I in column 1) do not include zonisamide. The process for preparing the compounds is set forth beginning at column 8, line 30 of the reference. Solvents for the production of the compounds are disclosed at column 9, lines 27-51, including dichloroethane at column 9, line 36.

However, the reference fails to disclose or suggest zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane, to which the present invention is directed.

Shirai et al., which is commonly assigned with the present application, discloses masking the unpleasant taste of a drug by coating a core containing the drug with a film layer containing ethylcellulose and a water-soluble substance. The drugs include zonisamide (column 3, line 20).

However, there is no disclosure or suggestion in the reference of zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane.

Bernstein et al. discloses heterocyclic amide derivatives of formula I in column 1 (which does not include zonisamide). The process for preparing the compounds of formula I is set forth in the disclosure beginning at column 9, line 65. Dichloroethane is specifically mentioned (column 14, line 34) as an example of a suitable solvent for preparing some of the compounds within the scope of formula I.

However, the reference fails to disclose or suggest zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane.

Nagamoto et al. discloses the administration of zonisamide in a solvent mixture consisting of propylene glycol, ethanol and saline.

The reference fails to disclose or suggest zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane.

#### **Summary**

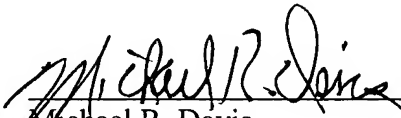
In summary, none of the references on the attached PTO-1449 form discloses or suggest zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane, nor do the references disclose or suggest a process for the preparation of such zonisamide crystals starting from zonisamide crystals containing residual 1,2-dichloroethane of more than 5 ppm. Accordingly, all of claims in the present application are considered to be patentable over these references.

It is Applicants' position that none of these references discloses zonisamide crystals containing not more than 5 ppm of residual 1,2-dichloroethane, or a process for producing such zonisamide crystals, to which the present invention is directed.

5. [X] A foreign patent office search report (International Search Report issued in the PCT application corresponding to the present application) citing one or more of the references is enclosed.

Respectfully submitted,

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December 12, 2003

FORM PTO 1449 (modified)

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICELIST OF REFERENCES CITED BY APPLICANT(S)  
(Use several sheets if necessary)

Date Submitted to PTO: December 12, 2003

ATTY DOCKET NO.  
2003-1812SERIAL NO.  
NEWAPPLICANT  
Yoshikazu UENO et al.FILING DATE  
December 12, 2003

GROUP

## U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	2003/0054041	3/2003	Lemmens et al.			
	AB	2003/0036556	2/2003	Jennings			
	AC	5,811,547	9/1998	Nakamichi et al.			
	AD	5,786,374	7/1998	Farooq et al.			
	AE	5,082,669	1/1992	Shirai et al.			
	AF	5,030,643	7/1991	Bernstein et al.			
	AG	4,172,896	10/1979	Uno et al.			
	AH	4,533,764	8/1985	Chang et al.			
	AI						

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO	
	AJ	03/020708	3/2003	WO				
	AK	63-150220	6/1988	Japan				
	AL	2 428 033	1/1980	France				
	AM	54-163570	12/1979	Japan				
	AN	53-77057	7/1978	Japan				

## OTHER DOCUMENT(S) (Including Author, Title, Date, Pertinent Pages, Etc.)

	AO	Lisgarten et al., "The structure of (1,2-Benzisoxazol-3-yl)methanesulfonamide: A Novel Antiepileptic Drug", Acta Cryst., C44, pages 2013-2016, 1988.
	AP	I. Nagamoto et al., "A Solvent Used for Antiepileptic Drugs Increases Serum and Brain Zonisamide Concentrations Seizure-Susceptible EL Mice", Epilepsy & Behavior, 2, 357-362 (2001).
	AQ	Hitoshi Uno et al., "Studies on 3-Substituted 1,2-Benzisoxazole Derivatives. V <sup>1)</sup> Electrophilic Substitutions of 1,2-Benzisoxazole-3-acetic Acid", Chem. Pharm. Bull., Vol. 26, No. 11, pages 3498-3503, 1978.

EXAMINER

DATE CONSIDERED



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	AF						
	AG						
	AH						
	AI						

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO	
	AJ	54-163823	12/1979	Japan				
	AK							
	AL							
	AM							
	AN							

## OTHER DOCUMENT(S) (Including Author, Title, Date, Pertinent Pages, Etc.)

	AO	Hitoshi Uno et al., "Studies on 3-Substituted 1,2-Benzisoxazole Derivatives. 6. Synthesis of 3-(Sulfamoylmethyl)-, benzisoxazole Derivatives and Their Anticonvulsant Activities", Journal of Medicinal Chemistry, Vol. 22, No. 2, pages 180-183, 1979.
	AP	Masanao Shimizu et al., "Research and Development of Zonisamide, a New Type of Antiepileptic Drug", Yakugaku Zasshi, Vol. 116, No. 7, pages 533-547, 1996.
	AQ	"Impurities: Guideline for Residual Solvents", ICH Harmonised Tripartite Guideline, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, pages 1-16, July 17 1997.

EXAMINER

DATE CONSIDERED